Remarks

In the specification, the paragraph beginning at page 5, line 20, has been amended to correct a minor typographical error. No new matter is added. Support for the amendment is in the specification at page 5, lines 4-7 (emphasis added):

> In the use of odorants *to stimulate or decrease vaginal flow*, it is preferred that the subject *individual is presented with the odorant at a suprathreshold concentration* (e.g., about 25-55 decismel units), but not irritative level, and inhales the odorant for about 1-3 minutes.

Reconsideration of the pending Claims 24, 25, 28, 29, 31-33, 35, 36, 38, 41, 42, 45, and 46 is respectfully requested.

The allowance of Claims 41 and 42 is gratefully acknowledged.

The objection to Claims 32 and 33 is also acknowledged.

Claims 27 and 30 have been canceled.

Claims 24, 25, 28, 29, 31, 32, 35, 41, and 45 have been amended to better define the subject matter claimed.

Support for the phrase "concentration of the odorants being greater than an average normal threshold concentration of the odorants...at about 25-55 decismel units" is in original Claims 16-17 (and 9-10) *("16. The article of manufacture of claim 14, wherein the concentration of the odorant is effective to provide a suprathreshold but not irritant amount of the odorant. 17. The article of manufacture of claim 16, wherein the concentration of the odorant is at about 25-55 decismel units.)*.

Further support for the amendments is in the specification at page 5, lines 3-6 ("In the use of odorants to stimulate or decrease vaginal flow, it is preferred that the subject individual is *presented with the odorant at a suprathreshold concentration (e.g., about 25-55 decismel units)*, but not irritative level, and inhales the odorant for about 1-3 minutes."), page 5, lines 7-9 ("An odorant is presented at a *suprathreshold level when the decismel level or concentration of the odorant is beyond that needed to be detected by a normosmic individual.")*, page 6, lines 18-20 ("In the art, a *"normosmic" individual is one who can detect the odor of a substance without irritant sensations when the odorant is presented within the range of its average normal threshold. ")*. In addition, the Examiner is directed to the specification at page 6, lines 10-11 ("Ranges of the *average normal threshold* for various odorant substances can be found in the art, for example, Amoore and O'Neill,...").

The Examiner is also directed to the discussion below regarding the understanding in the art of the term "suprathreshold' as being a concentration of odorants that is greater than the mean

or average normal threshold concentration of an odorant substance – a concentration of about 25-55 decismels being an increased amount of the mean normal threshold concentration.

No new matter has been added with the amendments, which are clearly supported in the specification as originally filed, as provided above. The amendments are intended to merely clarify language used in the claims and/or the subject matter claimed, and the scope of the claims is intended to be the same as after the amendments as it was before the amendments.

Rejection of Claims under 35 U.S.C. § 112(1)

The Examiner rejected Claim 25 under Section 112(1), on the basis that the phrase "separately packaged elements" for elements (i)-(iii) is not supported in the specification.

The Examiner is respectfully directed to the specification at page 7, lines 19-21, which states as follows:

> ...The various parts of the kit can be packaged separately and contained within a box or other packaging material.

Although Applicant submits that the objected to phrase is fully supported in the specification, to expedite prosecution, the phrase has been removed from the claim.

Such amendment is not to be considered as limiting the breadth of the claim.

Accordingly, it is submitted that the claims fully comply with the requirements of Section 112, and withdrawal of this rejection of the claims is respectfully requested.

Rejection of Claims under 35 U.S.C. 102(b)

The Examiner maintains the rejection of Claims 24, 27-30, 35, 36, 38, 45, and 46 as anticipated by the International Product Alert (IPA) bulletin entitled "Poan Washable Cold Cream Manufacturere: Kurabara Honpo Category: Beauty Skin Care" (01 June 1994 - PROMT Abstract), or by McMath from Adweek's Marketing Week entitled "The Skin Trade Goes Natural" (27 August 1990 -PROMT Abstract). At page 4, the Examiner also maintains the rejection of Claims 24, 27-31, 35, 36, 38, 45, and 46 as obvious over the IPA bulletin and McMath. Insofar as these rejections are maintained with respect to the claims as amended, these rejections are respectfully traversed.

The Examiner maintains that the cited commercial cream products would inherently contain the recited odorant mixtures at a suprathreshold but not irritant level – because the

cucumber and licorice extracts in the commercial skin creams would inherently be within *a level detectable by a normosmic individual – and within the claimed decismel level* and/or *at a suprathreshold but not irritant concentration*. The Examiner bases this assertion on Applicant's disclosure in the specification at page 5, lines 8-19. See the Office Action at page 3, 2nd paragraph (emphasis added):

> Each of the cited references teach skin creams comprising cucumber and licorice extracts therein...The cited commercial cream products would...also be inherently within the claimed levels – e.g., the products would inherently provide a suprathreshold but not irritant amount of the odorant (i.e., *based upon the definition provided on page 5, lines 8-19, of the instant specification*, the natural cucumber and licorice extract odors within the cited commercial skin creams would inherently be within a level detectable by a normosmic individual but not at a level so high or intense that it would be perceived as noxious or painful – thus, also within the claimed decismel level, within a suprathreshold but not irritant concentration, and/or at a concentration up to a suprathreshold but not irritant concentration, as claimed)...

Claims 24 and 35 have been amended to recite that the odorant composition is a *liquid*, and Claim 45 has been amended to recite that the odorant composition is in the form of *microcapsules* contained in a scratch-and-sniff odor patch. By comparison, the cited references describe a *cream* – and none of the delivery devices recited in the claims.

Claims 24, 25, 35, and 45 have also been amended to more clearly recite the concentration of the odorants in the composition – by clarifying and further distinguishing the term "suprathreshold concentration" in the claims.

A "suprathreshold" amount of an odorant is *not* merely the level detectable by a normosmic individual. A "suprathreshold concentration" is, *by definition*, a concentration that is *higher than* the average normal threshold concentration of an odorant – and, as recited in the claims, is at about 25-55 decismel units – a concentration that is many times higher than the average normal threshold concentration of the odorants.

The Examiner is directed to the supporting passages provided above for this amendment to the claims. In particular, the Examiner is directed to original Claims 16-17, which state as follows:

> 16. The article of manufacture of claim 14, wherein the concentration of the odorant is effective to provide a suprathreshold but not irritant amount of the odorant.
>
> 17. The article of manufacture *of claim 16*, wherein the concentration of the odorant is at about 25-55 decismel units.

A suprathreshold concentration is a definitive amount of the odorant – which can be objectively measured by known methods in the art. It is not merely the level detectable by a normosmic individual. It is a level that is *above* the average normal threshold concentration of an odorant. And in the instant claims – this is a level that is at 25-55 decismel units – where the normal threshold concentration is set at 0 decismel units, and thus, a concentration that is many times higher than the average or mean normal threshold concentration of the odorants.

Aside from Applicant's disclosure (as discussed above with regard to the claim amendments), the Examiner is respectfully directed to the disclosures in the following publications (copy enclosed) for a further supporting description of a suprathreshold concentration of an odorant – and the meaning of a decismel unit in the suprathreshold range in relation to the average threshold concentration of an odorant – as known in the art.

The decismel units in the suprathreshold range are an "X"-fold increase over the mean or average normal threshold concentration of an odorant. The Examiner is respectfully directed to the following (emphasis added):

a) **USP 6,325,475** (Hayes et al.; "Devices for Presenting Airborne Materials to the Nose") at col. 8, lines 54-66, and col. 20 at lines 55-65 (emphasis added):

...For threshold testing of the sense of smell, ***3-4 orders of magnitude*** dynamic range (***60-80 decismels***), where:

$$1 \text{ decismel} = \frac{\log 10 \text{ [odor concentration]}}{20}$$

are needed.

...

For a typical logarithmic series of test substance intensities, the dispensers 12 can dispense increasing masses of test substance by increasing the number of drops dispensed. Jetting at 1 to 10,000 drops/second, a single jet 12 can dispense over a 4 log-unit range of test substance intensity in 1 second. For greater temporal compression, jets 12 with differing concentrations can be used. For most test substances, **a range of 40 decismels (100-fold concentration range)** includes the thresholds of about 98% of all subjects (i.e., .+-.2 standard deviations), so that 80 decismels (10,000-fold) is more than an adequate dynamic range for the system.

b) **USP 5,380,765** (Hirsch;"Chemosensory olfactory assay for psychiatric disorders") at cols. 7-8, bridging paragraph (emphasis added):

Odor thresholds are expressed on the "decismel scale". **The mean threshold concentration of a chemosensory agent detected by a control group of 20-year olds is set at the 0 value.** A decismel is calculated by dividing the concentration of the chemosensory agent detected by the patient to the **normal threshold concentration** (using the published value or empirically determining the value) and then taking the logarithm of the quotient. The logarithm of the quotient is then multiplied by 20 to obtain the decismel value... **An increase in the threshold concentration value over the mean threshold concentration value of twofold corresponds to 6 decismels.** The suggested thresholds

> for hyposmia are 30 ds and of functional anosmia at 54 ds. The normal mean threshold values for each chemosensory agent are known and can be used to convert the threshold concentration into decismels. ...,

c) Prudhomme et al., Acute-Onset Persistent Olfactory Deficit Resulting from Multiple Overexposures to Ammonia Vapor at Work, *J Am Board Fam Pract* 11(1):66-69 (1998) (www.medscape.com/viewarticle/417766 at page 3 of 4 (emphasis added):

> * Decismels (dS) are defined as 20 log (test concentration/reference concentration), where the reference concentration is the average odor threshold in a reference population. Thus, a score of **40 dS indicates that the patient's odor detection threshold was at a test concentration 100 times the population average for the compound employed.**

As noted above, 6 decismels corresponds to a 2-fold increase over the mean or average threshold concentration value. Forty (40) decismels corresponds to a concentration that is 100 times the average odor threshold. Thus, the "25-55 decismel units" amount recited in the claims is *much higher* than the mean or average threshold concentration of the odorants.

The Poan and McMath compositions are *creams* – and the descriptions of the Poan and the McMath creams merely provides a list of several ingredients – with no recited concentrations – or delivery systems as recited in the claims.

There is no teaching in either reference that either product contains a *suprathreshold amount* of a cucumber and licorice odorant — i.e., a concentration of the odorant that is beyond the mean (average) normal threshold concentration at the recited decismel units. Nor is there any motivation for either product to be prepared with such a concentration of odorants as provided in Applicant's composition.

The cream products described by the cited references would not inherently contain the odorants in a *suprathreshold amount* as recited in the claims, and would not inherently provide the recited effect of altering blood flow to the vagina of the female.

The cited references do not teach or suggest an article of manufacture as claimed by Applicant comprising a suprathreshold but not irritating concentration of an odorant composition to alter blood flow to the vagina when inhaled by a female individual. Rather, the cited references merely teach a cream product that contains cucumber and licorice extracts in amounts to provide a moisturizing effect on the skin.

Accordingly, withdrawal of the rejection of the claims based on the cited references is respectfully requested.

Rejection of Claims under 35 U.S.C. 103(a)

The Examiner maintained the rejection of Claim 25 as obvious over the Drug & Cosmetic Industry (D&C.I.) publication entitled "Scentual Response" (Jan 1996, from PROMT database). This rejection is respectfully traversed.

The Examiner cites the publication as disclosing a report by the inventor, Dr. Alan Hirsch, that various odorants including a combination of lavender and pumpkin pie odorants caused increased penile blood flow.

The Examiner stated as follows:

> Claim 25 stands rejected ...as being unpatentable over the Drug & Cosmetic Industry publication entitled "Scentual Response" (Jan 1996, from PROMT database) for the reasons set forth in the previous Office action which are restated below.
>
> The cited reference discloses that Dr. Alan Hirsch....reported...that various odorants including the combination of lavender and pumpkin pie caused increased penile blow [sic] flow (see last paragraph).
>
> It would have been obvious to one of ordinary skill in the art at the time of the claimed invention was made to provide an article of manufacturer [sic] comprising a blood-flow effective amount of an odorant, ***whereby the odorant is a mixture of lavender and pumpkin pie***, based on the beneficial teachings provided by Dr. Hirsch within the cited reference.

The cited reference states as follows:

> On a back-to-the-farm note, Dr. Alan Hirsch of the Smell & Taste Treatment and Research Foundation (University of Chicago) reported to the American Psychosomatic Society that the odors of **pumpkin pie**, doughnuts, licorice and **lavender** significantly increased blood flow to the penis, the basis of an erection. The most potent was a combination of **lavender** and **pumpkin pie** which, if you can believe it, increased penile blood flow by 40 percent...

Claim 25 has been amended to recite that the odorant composition is a mixture of licorice-based and banana nut bread odorants, a mixture of licorice-based and cucumber odorants, or a mixture of baby powder and chocolate odorants.

The cited publication does not teach or suggest an article of manufacture in which the odorant composition is one of the recited mixtures of odorants as claimed.

Nor does the cited publication teach or suggest an article of manufacture as recited in Claim 25 composed of an odorant composition and the listed elements in combination.

Accordingly, withdrawal of the rejection of Claim 25 is respectfully requested.

Rejection of Claims for Double Patenting

The Examiner maintained the rejection of Claim 25 on the basis of double patenting in view of Claims 22-23 of USP 5,885,614.

The relevant claims (16, 19, 22-23) of USP 5,885,614 are as follows:

16. A method of increasing penile blood flow in a male individual, comprising:

...

the odorant selected from the group consisting of orange, a mixture of lavender and pumpkin pie, a mixture of doughnut and black licorice, a mixture of pumpkin pie and doughnut, lily of the valley, black licorice, a mixture of doughnut and cola, a mixture of black licorice and cola, a mixture of lavender and doughnut, chocolate, strawberry, rose, green apple, parsley, peppermint, musk, lavender, vanilla, cranberry, pink grapefruit, floral, baby powder, oriental spice, cinnamon buns, roasting meat, cheese pizza, doughnut, cola, pumpkin pie, and buttered popcorn.

19. A method of increasing penile blood flow in a male individual, comprising:

...

the odorant selected from the group consisting of orange, a mixture of lavender and pumpkin pie, a mixture of doughnut and black licorice, a mixture of pumpkin pie and doughnut, lily of the valley, black licorice, a mixture of doughnut and cola, a mixture of black licorice and cola, and a mixture of lavender and doughnut.

22. An article of manufacture, comprising:
(a) an odorant as recited in **claim 16** and packaged in a recited form, wherein the odorant when inhaled by a male individual is effective to increase penile blood flow; and
(b) instructions for use of the odorant according to the method of claim 16.

23. An article of manufacture, comprising:
(a) an odorant as recited in **claim 19** and packaged in a recited form, wherein the odorant when inhaled by a male individual is effective to increase penile blood flow; and
(b) instructions for use of the odorant according to the method of claim 19 .

It is believed that Claim 25 as amended clearly distinguishes over Claims 22-23 of USP 5,885,614. Accordingly, withdrawal of this rejection is respectfully requested.

Claim Objections/Allowable Claims

As suggested by the Examiner, Claim 32 has been amended to incorporate the limitations of the base claim (Claim 24) and the intervening claims (Claim 31). Accordingly, withdrawal of the rejection of Claim 32 is respectfully requested.

The allowance of Claims 41 and 42 is again acknowledged.

Extension of Term. The proceedings herein are for a patent application and the provisions of 37 CFR § 1.136 apply. Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that Applicant has inadvertently overlooked the need for a petition for extension of time. If any extension and/or fee are required, please charge Account No. 23-2053.

Applicant believes that the claims are in condition for allowance, and notification to that effect is respectfully requested. The Examiner is urged to telephone the undersigned Attorney if any questions should arise or further discussion would expedite the examination of the application.

Respectfully submitted,

Dated: _____, 2005

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APPENDIX

Copies of cited publications (relevant pages):

USP 6,324,475 (Hayes) – cols. 7-8 and 19-20

USP 5,380,765 (Hirsch) – cols. 7-8

Prudhomme (1998) – pages 1 and 3

FIG. 21 is a plot of threshold data using an ink-jet-based digital dispenser according to the present invention;

FIG. 22 is a schematic view of a long and short duration olfactory stimulus from an ink-jet based digital dispenser according to the present invention;

FIG. 23A is a schematic view of microreservoirs and manifolds attached to six parallel ink-jet channels;

FIG. 23B is a schematic view of an upper layer of a laser etched plate forming manifolds for the ink-jet channels shown in FIG. 23A;

FIG. 23C is a schematic view of a lower layer of a laser etched plate forming reservoirs for the ink-jet channels shown in FIG. 23A;

FIG. 24 shows human subject threshold tests for left, right and left and right combined nostrils conducted on the ink-jet-based digital dispenser illustrated schematically in FIGS. 3A and 3B;

FIG. 25 shows human subject threshold tests for left, right and left and right combined nostrils conducted on the ink-jet-based digital dispenser illustrated schematically in FIGS. 3A and 3B;

FIG. 26 is a schematic view of the dispersion of an olfactant in an airtube; and

FIG. 27 is a graph of the concentration of an olfactant versus time at 0.005 m from the source of the olfactant.

DESCRIPTION OF THE PREFERRED EMBODIMENT

As shown schematically in FIGS. 1A and 1B, the digital dispenser 10 of the present invention includes ink-jet microdispenser technology by incorporating piezoelectric transducer jets 12 which may be formed of piezoelectric material such as lead zirconate titanate (PZT). Those of ordinary skill in the art will recognize, however, that the piezoelectric transducer can be replaced by other transducers such as electrostrictive transducers, magnetostrictive transducers and electromechanical transducers. As shown in FIG. 1B, the digital dispenser 10 preferably includes eight piezoelectric microdispensing channels 12.

The test substances may be dispensed from reservoirs 16 in which test substance volume dispensing resolution preferably will be in the range of 200 picoliters. The test substances may include drugs, fragrances and volatile component containing substances. The test substances may also include nicotine for use in a cigarette withdrawal regimen.

The piezoelectric microdispensers 12 are integrated into individual, modular mechanical and hydraulic assemblies. These assemblies in turn are integrated into the airborne material delivery system. Conventional control electronics 14 and software design well known to those of ordinary skill in the art for use in solder microdispensing are used in the digital dispenser 10. The digital dispenser 10 according to the present invention permits the optimization of microdispenser operating parameters in terms of waveform and frequency for the airborne material/vehicle combinations.

According to a preferred embodiment of the present invention, water, ethanol and propylene glycol are used as the fluid vehicles for low concentration airborne material dispensing. All the test substances of interest are soluble in water, ethanol or propylene glycol, and none of the vehicles will interfere with olfactory thresholds for the 10 to 1000 picoliter dispensing volumes employed by the digital dispenser 10 of the present invention. The surface tensions and viscosities (magnitude and Newtonian vs. non-Newtonian) of the pure test substance solutions to be used are within the range such that their dispensing performance will be acceptable.

A schematic of the functional elements of the microdispensing device 12 of the digital dispenser 10 of the present invention is shown in FIG. 1C. As shown in FIG. 1C, the micro-dispensing device 12 incorporated in the device of the present invention includes a fluid fitting 18, a piezoelectric crystal 20, a glass tube 22 and an orifice nozzle 24. The fabrication technology and processes as well as the operating characteristics of this type of device are disclosed and claimed in U.S. Pat. Nos. 5,227,813, 5,235,352, 5,334,415, 5,345,256, 5,365,645, 5,373,314, 5,400,064, 5,402,162, 5,406,319, 5,414,916, 5,426,455, 5,430,470, 5,433,809, 5,435,060, 5,436,648 and 5,444,467, the entire disclosures of which are hereby incorporated herein by reference. The functional elements of the micro-dispensing device 12 of the digital dispenser 10 of the present invention as shown in FIG. 1C are integrated into a housing 26 that includes a fluid fitting as shown in FIG. 1A. This assembly is installed into a mechanical assembly that includes an electrical connector, fluid reservoir 16, and fluid filter. It also provides the mechanical reference surfaces for mating with the digital dispenser 10 of the present invention.

Airflow in the direction of the arrows shown in FIG. 1A is passive and is controlled by a subject's sniff or inhalation. The interface 28 to a subject preferably is similar to the output of a nasal inhaler, with one output for each nostril, although the interface may also have a single output for both nostrils. The total air volume for each channel preferably is less than 200 ml to insure that all of the airborne material is inhaled during a sniff (average of 0.5 liter/second flow rate during a 0.5 second sniff). Preferably a fan (not shown) and an activated charcoal filter 32 will be attached to the inlet 34 of the device 10 to provide a brief air purge to remove any residual test substance from the system between trials.

The dispensers 12 are targeted onto heated screens 36, preferably formed of platinum, to vaporize the test substance and vehicle. Preferably the platinum screens 36 are heated during the air purge between trials. A water dispenser 30 can be activated to humidify the air. Also, it is preferred that two heated platinum screens 36 are used to allow binasal testing.

If required, an aerosol blocking filter 38 may be included to filter aerosol particles (larger than 1 μm) that might be generated during high frequency multiple droplet dispensing events, due to later droplets impacting into a pool.

In a preferred embodiment, the digital dispenser 10 includes eight droplet generators. Each micro-dispensing device 12 is evaluated in a test stand with isopropanol being used as a test fluid. Droplet size and velocity as a function of drive voltage and frequency are measured for several frequencies. Droplet velocity is measured by stroboscopically "freezing" the drops in space and measuring the droplet-to-droplet distance ($V=f\lambda$) through a microscope. Drop size is measured by measuring the flow rate of the drop stream over a precise time interval.

Each test substance/vehicle solution of interest is tested for its microdispensing performance in the test stand over a range of concentrations. For threshold testing of the sense of smell, 3-4 orders of magnitude dynamic range (60-80 decismels), where:

$$1\ \text{decismel} = \frac{\log 10\ [\text{odor concentration}]}{20}$$

are needed. This is achieved by a combination of varying the concentration of the test substance in the vehicle and varying the amount dispensed. For example, the delivered mass requirements of one olfactory stimulation could require

APPENDIX – RESPONSE USSN 09/707,655

15–25 up and down intensity steps for a given threshold test, with a maximum of 3 threshold tests per subject.

Fragrances will be presented by microdispensing miniscule amounts into the vapor a subject is asked to sniff. Five minute breaks will be given between tests (more frequently if requested), and no more than 45–60 minutes total testing will be done per subject.

The subject population at SMU will be drawn from the entire student body, which is 95% between the ages of 17 and 23, 52% female, and 22% minorities, of whom approximately 10% are African American, and the remainder are predominantly of Hispanic, Asian, and Native American origin.

The subject population at UC-Irvine will be drawn from normal and Alzheimer's diseased aged subjects, ranging from 55 to 85 years of age. This group is approximately 50% female.

EXAMPLE 4

The digital dispenser **10** of the present invention will permit the probing of new dimensions of human olfaction. The analytical capability of the digital dispenser **10** can be used to understand how olfactory signals are summed over time (to the millisecond range) and (when combined with endoscopic presentation) over the space of the olfactory epithelium. Thus, presenting brief "clouds" of airborne molecules or droplets allows exploration of the temporal integration (approximately 100 ms) and, with endoscopic systems, the spatial integration (approximately 10,000 to 100,000 square microns of olfactory epithelium or the vomeronasal organ) of sensory responsiveness of the olfactory epithelium and the vomeronasal organ (which is specially tuned to pheromones).

The resolution of these basic psychophysical issues will allow the determination of the most reliable and most useful patterns to use for diagnostic work. By injecting miniature "clouds" of airborne molecules or droplets into the inspired airstream, olfactory stimuli can be delivered that are very brief, relative to the overall duration of a voluntary sniff (about 0.5 seconds in duration) or an inhalation (2–4 second duration). This is shown schematically in FIG. **22**. Actual examples of such temporal "sculpting" of the gas stimulus are shown in FIG. **7**. There will be some smoothing of these temporal functions, due to turbulence as air flows through the nasal meatuses and around the turbinate bones. Retention and release of test substance molecules on the airway surfaces will also produce some temporal smearing of the olfactory stimulus. Still, a temporal dimension will be introduced into olfactory testing by the microdispensing of airborne molecules or droplets into the inlet of the nostrils.

The digital dispenser **10** of the present invention will allow a determination of empirical data such as what temporal patterns of stimulation during a single sniff or single inhalation give the strongest subjective response (i.e., lowest "threshold" or largest d' of a Receiver Operating Curve), how responses from the two nostrils are integrated, what the time-constants are for inter-nostril integration, whether there is an olfactory directional sense, whether there is a dominant hemisphere when dissimilar airborne materials are presented to the two nostrils, whether there is a directionality of olfactory signals due to inter-nostrils differences, whether concentration and duration will be interchangeable (for a fixed total number of airborne materials) over about 600 milliseconds, with little further integration thereafter and whether different airborne materials give different integration functions, as is the case with different adaptation functions for different airborne materials.

The results of these determinations will yield a normative baseline for novel areas of human performance that will provide sensitive indicators of neuropathology. The digital dispenser can be configured as a hand-held device to be used by a clinician in the office (or even in the field) that can precisely probe for within and between nostrils effects. In view of the possibility that olfactory asymmetries could be useful predictors of brain disease, these studies could lead to a practical and powerful olfactory diagnostic tool.

The choice of test substances to be loaded in the microjets **12** include, but are not limited to, pyridine, eugenol, 1-butanol and mercaptan which are commercially available from International Flavors and Fragrances, Inc. as well as some test substances shown to be especially difficult to identify for patients with Parkinson's and Alzheimer's such as cinnamon, chocolate, strawberry and pizza which are commercially available from 3M Microfragrances. Other test substances are disclosed in Table 3 in Amoore, J. E. (1991): Specific anosmias in *Smell and Taste in Health and Disease*, ed. by T. V. Getchell et al., Raven Press, New York, pp. 655–664, the entire disclosure of which is incorporated herein. These other substances include: fruity (isoamyl acetate), etherish (methyl ethyl ketone), camphor (1,8-cineole), clove (eugenol), cinnamon (cinnamaldehyde), minty (1-carvone), thyme (thymol), rosy (2-phenylethyl alcohol), citrous (geranial), floral (phenylethyl methyl ethyl carbinol), lily (lyral), violet (B-ionone), vanilla (vanillin), amber (thujamber), musky (w-pentadecalactone), garlic (allicin), fishy (trimethylamine), halugen (iodoform), burnt (pyridine), phenolic (4-ethylphenol), sweaty (isovaleric acid), urinous (5a-androst-16-en-3-one), repulsive (phenylisocyanide), spermous (1-pyrroline), fecal (skatole), resinous (isoamyl alcohol), gassy (tert-butyl mercaptan), acid (acetic acid), buttery (2,3-butanedione), earthy (2-methylisoborneol), vegetable (methional), cyanide (hydrogen cyanide), malty isobutyraldehyde), sulfide (hydrogen sulfide) and armpit (trans-3-Methyl-2-hexenoic acid).

Still other test substances include: peanut, soap, paint thinner, motor oil, smoke, lemon, menthol, onion, licorice, wintergreen, orange, lilac, grape, gasoline, bubble gum, chocolate, mint, root beer, cherry, strawberry, fruit punch, rose, turpentine, pine, pizza, watermelon, grass, natural gas, cinnamon, pineapple, coconut, dill pickle, clove, banana, garlic, peach, lime, leather, gingerbread, cheddar cheese, musk, cedar, apple, black pepper, chili, tomato, pumpkin pie, skunk, whiskey and honey.

The concentration of test substance and the temporal envelope of presentation, as well as the inter-nostrils differences can all be controlled by merely changing the number of digitally-controlled microdrops to be dispensed into the airstream. In all cases, the maximum mass of airborne materials injected into the airstream will be kept well below the saturation point, so that condensation of the test substances onto the air passages will be minimized.

For a typical logarithmic series of test substance intensities, the dispensers **12** can dispense increasing masses of test substance by increasing the number of drops dispensed. Jetting at 1 to 10,000 drops/second, a single jet **12** can dispense over a 4 log-unit range of test substance intensity in 1 second. For greater temporal compression, jets **12** with differing concentrations can be used. For most test substances, a range of 40 decismels (100-fold concentration range) includes the thresholds of about 98% of all subjects (i.e., ±2 standard deviations), so that 80 decismels (10,000-fold) is more than an adequate dynamic range for the system.

The test subjects will hear an audible "beep," informing them to start an inhalation (or sniff), and the airborne

APPENDIX – RESPONSE USSN 09/707,655

tification and sensitivity to 40 stimuli using scratch and sniff cards. Each subject rated the fragrance samples by scratching with a pencil included with the test cards, sniffing, and then identifying the odorant as one of four choices. A label could be repeatedly scratched as needed before moving to the next odorant and returning to previous odors was allowed.

The results of the patient's score on the Smell Identification Test™ were evaluated by reference to the established normal values for age and gender provided in the *Smell Identification Test™ Administration Manual* on pages 19 and 20. The patient's total number of correct responses (maximum of 40) was established by use of the test's scoring key. The patient's test score is located in the far left hand column of Table 1 for women and Table 2 for men. The age group is located along the top of the table and the subject's percentile score is read at the intersection of test score row and age group column. The percentile value reflects the percentage of normal patients having that score.

A diagnosis for an olfactory dysfunction is made by identifying whether the person's test score falls within the anosmia (total inability to perceive odor) or microsomia range (decreased smell ability). Generally, scores falling in the following ranges are indicative of smell dysfunction:

Smell Identification Test Score	Olfactory Diagnosis
0-5	Probable malingering
6-19	Total anosmia
20-33	Microsomia (males only)
20-34	Microsomia (females only)
34-40	Normosmia (males only)
35-40	Normosmia (females only)

The unilateral threshold test was conducted according to standard methods as described by J. Amoore et al., *Rhinology*, 21:49-54 (1983). Briefly, the patient's ability to detect increasing amounts of carbinol, PD-lactone, cineole, thiophane, pyridine, (PE-phenol), and CA-phenone in the left and right nostrils was tested. The standards in decismels were obtained from OlfactoLabs, El Cerrito, Calif. For example, the threshold level of PE phenol detected by a patient was determined by presenting the patient with 64 different bottles of different concentrations of PE-phenol. The patients were presented with bottles of different concentrations compared to the blank and asked to identify the bottle with the substance. The patient was presented with the bottles in random order and needed to correctly identify the substance three times in order to identify the patient's threshold concentration. The level at which the patients in the study detected each of the compounds was compared to known or expected values. The standard samples from OlfactoLabs were already calibrated in decismels. If the amount detected by the patient was lower than the expected values, the patient was more sensitive to the compound and detected the chemosensory agent at a negative decismel value. If the amount detected known was greater than the expected value, the patient was less sensitive to the compound and detected the chemosensory agent at a positive decismel value.

Odor thresholds are expressed on the "decismel scale". The mean threshold concentration of a chemosensory agent detected by a control group of 20-year olds is set at the 0 value. A decismel is calculated by dividing the concentration of the chemosensory agent detected by the patient to the normal threshold concentration (using the published value or empirically determining the value) and then taking the logarithm of the quotient. The logarithm of the quotient is then multiplied by 20 to obtain the decismel value. Decismel values can be positive or negative. A positive decismel value indicates the patient is less sensitive to the chemosensory agent, i.e. has a higher threshold detection concentration. A negative decismel value indicates that the patient is more sensitive to the compound, i.e. has a lower threshold detection concentration. An increase in the threshold concentration value over the mean threshold concentration value of twofold corresponds to 6 decismels. The suggested thresholds for hyposmia are 30 ds and of functional anosmia at 54 ds. The normal mean threshold values for each chemosensory agent are known and can be used to convert the threshold concentration into decismels. A change of at least 5 ds from the expected value was considered a significant change in the threshold level of detection of the compound.

The Accusens T Test ® was conducted according to standard methods as described by the *Accusens T™ Taste Function Kit Manual*. Briefly, the ability of the patients to taste sodium chloride (NaCl), sucrose, hydrochloric acid (HCl), urea, and phenylthiocarbamide (PTC) was evaluated by the patients tasting solutions containing increasing amounts of the compound.

The ability of the patients to detect and recognize the type and intensity of the solution was measured. Two drops of each of three solutions was placed on a patient's tongue successively. Two of three solutions were water and one of the solutions was either salty (NaCl), sweet (sucrose), sour (HCl) and bitter (PTC). Three different concentrations of salt, sucrose and HCl were tested. The PTC test was the last test performed. The patient was instructed to identify which one of the three solutions was different, whether it was salty, sweet, sour or bitter, and to estimate the degree of the taste on a scale of 1 to 100. All three judgments must be correct for diagnosis of normal taste. If the patient could not detect correctly the different tastant or recognize each tastant, the next higher concentration of the tastants was tested in the same manner until the patient correctly identified the tastants. The patient's responses were compared to established values for normal taste detection and recognition provided in the test kit. Any failure to detect or recognize the tastants is indicative that the patient has hypogeusia.

If the patient correctly detects and recognizes all of the tastants but gives intensity responses less than 5%, then a second test is done. Patients taste each of three different concentrations of the NaCl solution, sucrose solution and HCl solution and rate the intensity of each of the solutions. Responses considered normal for the lowest concentration are 5% to 15%, responses considered normal for the middle concentration are 10% to 30% and responses considered normal for the highest concentration are 25% to 50%. Any response lower than the lower percentage of the ranges noted above is abnormal and indicative of hypogeusia.

The patients also were evaluated for psychiatric disorders using the MMPI-II, the MCMI-II, and the Beck Depression Inventory. The MMPI-II is available from National Computer Systems and is administered according to standard methodologies as described in *Psychological Assessment with the MMPI*, A. Friedman et al., editor, Laurence Erlbaum Assoc., publishers (1989) at

APPENDIX - RESPONSE USSN 09/707,655

Acute-Onset Persistent Olfactory Deficit Resulting from Multiple Overexposures to Ammonia Vapor at Work

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Introduction

Impaired olfaction (a functional decrement in the sense of smell) is not uncommon. It is estimated that at least 2 million Americans suffer from an impaired sense of smell, although the actual number is probably higher.[1] The importance of this primary sense should in no way be minimized, since its absence can result in profound consequences. Both personal protection and quality of life can be compromised by impaired olfaction. Intact olfaction provides an excellent warning system for detection of hazardous conditions including smoke from fires, ingestion of spoiled foods, and hazardous materials encountered on the job. An employee lacking intact olfaction could be seriously impaired in certain settings, and indeed might be precluded from selected duties as a result. Even appropriate respiratory protection (ie, air-purifying respirators) might not offer sufficient assurance against toxic exposures because the impaired person would not be able to detect respirator leaks or cartridge breakthrough.[2] The senses of taste and smell are intertwined; loss of smell can adversely affect gustatory pleasure or, more importantly, can lead to anorexia.

Despite the frequency of irritant upper airway exposures occupationally,[3] published cases of work-related residual olfactory impairment have frequently lacked documentation of sensory testing. Recognition of the link between irritant exposure and upper airway functional loss is thus important to occupational and general health practice.

We report a case in which persistent hyposmia (reduction in the sense of smell) occurred following an acute industrial exposure to ammonia.

Case Report

A 41-year-old man was in his usual state of good health until 1993, when he was acutely overexposed to an ammonia leak while employed as the owner-operator of a fish-processing plant. The aqueous ammonia involved in the leak was used as a refrigerant in the fish-processing operation. No other irritant gases, including sulfur dioxide, were used as refrigerants in the operation. At the time of the leak, the patient experienced eye and nasal irritation and mild facial skin burning. He avoided mouth breathing and denied experiencing any other acute respiratory symptoms. He spent an entire morning in the vicinity of the leak without wearing respiratory protection. He had previously experienced ammonia leaks with similar but less severe symptoms. No quantitative industrial hygiene measurements of the ammonia concentration were made.

In contrast to previous ammonia exposures, after this incident the patient's nasal symptoms persisted, marked by a sense of nasal stuffiness and intermittent epistaxis continuing for 2 weeks. Although the nasal congestion later resolved, he also complained of a concomitant, complete loss of smell that improved only minimally. Whereas some sense of smell did return, he noticed difficulty recognizing previously familiar odors, such as his wife's perfume or freshly mowed grass. Foul or unpleasant odors did not replace normal smells. No other nasal or respiratory tract symptoms, such as rhinorrhea or discharges, persisted. His sense of taste returned to baseline after a transient complaint of a metallic taste.

His senses of hearing and vision remained intact. He reported no history of atopic disease, including allergic rhinitis. He was a lifetime nonsmoker and was on no medications at the time of exposure. There was no history of nasal trauma related to his symptoms. He was examined by an otolaryngologist 6 months after the acute exposure; no structural abnormalities were observed. A brief trial of intranasal flunisolide was prescribed with no effect.

When he was examined 30 months after his acute exposure, his external nares were patent and without apparent abnormality. Bilateral nasal breathing was without deficit, and there was no sinus tenderness to palpation. Findings of the oropharynx and

chemically-induced olfactory dysfunction. More interestingly, of these 7 patients, 3 (43 percent) had the onset of their hyposmia following exposure to ammonia. Details of the exposure are briefly described for only one of the three incidents. In the described case, an acute, overwhelming ammonia exposure caused a severe intranasal burn and ultimately irreversible hyposmia. As in our case, there was no response to a trial of nasal steroids. This case series provides additional support that ammonia can adversely impact olfaction.

A syndrome known as the reactive upper airways dysfunction syndrome, or RUDS, might tangentially apply to our case. The syndrome helps categorize persons who experience persistent nasal symptoms, specifically rhinitis and heightened subjective sensitivity to chemical irritants, after a single acute exposure to an upper respiratory tract irritant.[30] This syndrome is considered analogous to an asthma-like syndrome known as RADS (reactive airways dysfunction syndrome) that develops in certain persons following acute pulmonary tract irritation.[31] Symptoms develop after a single (generally, intense) exposure and persist in the absence of additional exposures. Our patient did develop some pertinent nasal symptoms following one of multiple acute exposures to ammonia. Although an olfactory deficit as such has not been incorporated into the clinical syndrome definition of RUDS,[30] it is a plausible consequence of any persistent inflammatory process.

A major limitation in earlier reports of olfactory impairment following environmental exposure has been the lack of objective, standardized measurements of olfactory function. The two tests used in this case, UPSIT (University of Pennsylvania Smell Identification Test), a qualitative test kit, and OLFACTO-LABS (Quantitative Smell Test Kits) are well-validated[32,33] and are now widely available.

The upper respiratory tract is inherently susceptible to the toxic effects of airborne irritants. The nasal mucosa and olfactory epithelium are primary targets of water-soluble toxicants, of which ammonia is prototypic. Such exposures and their resulting impairment are likely far more commonly encountered in primary care settings than is generally appreciated. It has recently been reported, for example, that family physicians spend 14 percent of their time dealing with occupational health problems overall.[34] Upper airway disorders, including irritant-related symptoms, are an important occupational problem among those likely to be encountered. In the same study, 29 percent of physicians specified occupational exposures as a high-priority issue about which more knowledge was needed. Knowledge on olfactory impairment is a particularly needed area of better understanding.

* Decismels (dS) are defined as 20 log (test concentration/reference concentration), where the reference concentration is the average odor threshold in a reference population. Thus, a score of 40 dS indicates that the patient's odor detection threshold was at a test concentration 100 times the population average for the compound employed.

References

1. Davidson TM, Murphy C. Olfactory impairment. West J Med 1993;159:71-2.
2. Shusterman DJ, Sheedy JE. Occupational and environmental disorders of the special senses. Occup Med 1992;7:515-42.
3. Bascom R, Raford P. Upper airway disorders. In: Rosenstock L, Cullen MR, editors. Textbook of clinical occupational and environmental medicine. Philadelphia: WB Saunders, 1994:315.
4. Amoore JE. Effects of chemical exposure on olfaction in humans. In: Barrow CS, editor. Toxicology of the Nasal Passage. Washington, DC: Hemisphere Publishing, 1986:155-90.
5. Doty RL. A review of olfactory dysfunctions in man. Am J Otolaryngol 1979;1:57-79.
6. Halpern BP. Environmental factors affecting chemoreceptors: an overview. In: Hayes AW, editor. Toxicology of the eye, ear, and other special senses. New York: Raven Press; 1985:195-211.
7. Rose CS, Heywood PG, Costanzo RM. Olfactory impairment after chronic occupational cadmium exposure. J Occup Med 1992;34:600-5.
8. Ahlstrom R, Berglund B, Berglund U, Lindvall T, Wennberg A. Impaired odor perception in tank cleaners. Scand J Work Environ Health 1986;12:574-81.
9. Schwartz BS, Doty RL, Monroe C, Frye R, Barker S. Olfactory function in chemical workers exposed to acrylate and methacrylate vapors. Am J Public Health 1989;79:613-8.
10. Meyer J. Wie richt Blausäure? Gasmaske 1935;7:112.
11. Buchan RF. Industrial selenosis. Occup Med 1947;3:439-56.
12. Woelk HA. Die traumatische anosmie und ihre Begutachtung. Monatsschr Unfallheilk 1930;37:1-17.
13. MacIntyre I. Prolonged anosmia. Br Med J 1971;2:709.
14. vonPfander F. Anosmie durch einmaliges Einatmen von Schwefeldioxyd. HNO 1959;8:59-60.
15. Refrigeration. In: Kirk RE, Othmer DF, Grayson M, Eckroth D. Kirk-Othmer encyclopedia of chemical technology, vol 20. 3rd ed. New York: John Wiley & Sons; 1982:78-107.
16. Refrigerating plants. In: Parmeggiani L, technical editor. Encyclopaedia of occupational health and safety. 3rd rev ed. Geneva: International Labour Office, 1983:1910-2.
17. Occupational exposure to ammonia [criteria for a recommended standard].Rockville, Md: Department of Health, Education, and Welfare, Centers for Disease Control, National Institute for Occupational Safety and Health, 1974. (NIOSH publication no. 74-136.)
18. Environmental Health Criteria 54: Ammonia. Geneva: World Health Organization; 1986.
19. Toxicological profile for ammonia. Atlanta, Ga: Department of Health and Human Services; Public Health Service, Agency for Toxic Substances and Disease Registry, 1990.